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Towards global consensus on core outcomes for Hidradenitis Suppurativa research: An update from the HISTORIC consensus meetings I and II

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Competing interests statement

L. Emtestam, E. Prens, H.H. van der Zee and G.B.E. Jemec have been involved in the development of instruments that could potentially be used to measure the physical signs domain. Specific instruments were however not discussed.

What's already known about this topic?

- Reported outcome measure instruments for hidradenitis suppurativa (HS) are numerous and diverse with 30 instruments recently found in 12 randomised trials.
- This diverse use of instruments limits the possibility to perform evidence synthesis and may produce outcome reporting bias.
- A Core Outcomes Set (COS) is an agreed minimum set of outcomes that should be measured and reported in all clinical trials.

What does this study add?

- The study used an international and multi-stakeholder approach, involving patients, dermatologists, surgeons, the pharmaceutical industry and medical regulators.
- Two consensus meetings, in Europe and North America, considered potential HS core domains, within a nominal group theory structure
- Seven potential core domains were put forward to the subsequent online Delphi: disease course, physical signs, HS-specific quality of life, satisfaction, symptoms, pain, and global assessment.

Abstract

BackgroundA Core Outcomes Set (COS) is an agreed minimum set of outcomes that should be measured and reported in all clinical trials for a specific condition. Hidradenitis suppurativa (HS) has no agreed upon COS. A central aspect in the COS development process is to generate and prioritise a list of candidate items and domains. There is no existing gold standard methodology, but in most COS processes the domains are defined by the steering group. In this study, we used a modified approach in which the Delphi participants worked side by side on creating the domains at two consensus meetings. These meetings took place in September and October 2016 in Vienna and New York respectively and the results are reported here. **Objectives:**The main objectives were to consider which items from a long list of candidate items to exclude and which to cluster into outcome domains. **Methods:**The study used an international and multi-stakeholder approach, involving patients, dermatologists, surgeons, the pharmaceutical industry and medical regulators. The study format was a combination of formal presentations and small group work based on nominal group theory to generate consensus. **Results:**41 individuals from 13 countries and four continents participated. Nine items were excluded and there was consensus to propose seven domains: disease course, physical signs, HS-specific quality of life, satisfaction, symptoms, pain, and global assessment. **Conclusions:** The HISTORIC consensus meetings I and II will be followed by further online Delphi rounds to finalise the core domain set, building on the work of the in-person consensus meetings.

INTRODUCTION

Development of evidence-based and consensus-driven outcome measures are necessary to ensure that study results are comparable to permit meta-analyses and hence better inform healthcare decisions. In consequence, consensus on outcomes is a prerequisite for patients to receive the benefits of top level evidence based medicine. Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease, characterised by repeated outbreaks of painful inflamed nodules or boils in the apocrine gland-bearing regions (axillae, genital area, groin, breasts and perianal region).^{1,2} The estimated prevalence is 1-4 % worldwide.³⁻⁵ HS is associated with significant disability due to pain and subsequent loss of mobility.⁶ Interventions for HS are diverse and include topical treatment, systemic antibiotics, anti-inflammatory therapy, biologics and surgical therapy including laser surgery. There is a need for continuing research on therapies since the level of evidence for existing treatments is low, suggesting a particular need for trials.⁸

Clinical trials should have well-defined primary and secondary outcomes to answer questions generated by the main hypotheses. A Core Outcome Set (COS) is an agreed minimum set of outcomes that should be measured and reported in all clinical trials of a specific disease or trial population, a recommendation of *what* should be measured and reported in all clinical trials.⁹ Once a COS is defined, the next step is to achieve consensus on the instruments most suitable to measure each core domain.¹⁰ This selection process includes evaluation of the quality of the instruments, assessing their validity, reliability, responsiveness to change and feasibility.¹¹ Like most diseases, HS has no agreed upon COS and the reported outcome measure instruments are numerous. In a recent systematic review, the authors identified a total of 30 outcome measure instruments in 12 RCTs and the quality of studies looking at validity of the instruments was generally low.¹² Consequently trialists and researchers use various instruments, which may or may not be representative of the most important aspects of the disease. In addition, the heterogeneity and lack of consensus regarding use of outcome measure instruments limits the possibility to perform evidence synthesis, including meta-analysis,⁸ and likely leads to outcome reporting bias because of selective reporting of more favourable outcomes. Empirical evidence of this phenomenon has been highlighted in the literature.¹³

Based on these existing problems within HS outcome measures the Hidradenitis

Suppurative cORE outcomes set International Collaboration (HISTORIC) was formed as a collaboration between the International Dermatology Outcome Measures (IDEOM) initiative, the Cochrane Skin Group - Core Outcome Set Initiative (CSG-COUSIN) and Zealand University Hospital, Roskilde.

The first HISTORIC goal was to develop a COS for HS clinical trials, reducing the risk of heterogeneity in instruments and outcome reporting bias and ensuring that researchers report on outcomes that are relevant to all major stakeholders.^{14,15} The intention is that the COS for efficacy measures should help guide all HS clinical trials on a global basis, covering both medical and surgical trials.

A central aspect in the COS development process is to generate and prioritise a list of candidate items and domains. There is no existing gold standard methodology, but in most COS development processes the domains/outcomes are defined by the steering group based on results from literature reviews and qualitative studies in relevant stakeholder groups.¹⁶⁻¹⁸ In our COS development process, the steering group decided that a wider set of HS stakeholders should have the chance to vote by e-Delphi on 56 nominal items to help guide formation of candidate domains.

After the first two online Delphi rounds the Delphi participants were then invited to take part in two consensus meetings, where patients and health care professionals (HCPs) worked side by side on creating the domains together with members of the steering committee. This method permitted inclusion of opinions from a wider set of patients and other Delphi participants in the important phase of domain formation from candidate items. The consensus meetings took place in September and October 2016 in Vienna, and New York respectively, and the results are reported here.

Aims

The aims of the 1st consensus meeting were to:

- Review results of the first two online Delphi rounds
- Discuss whether any items could be removed from the list of potential items
- Discuss grouping of items into domains
- Discuss appropriate names for the created domains

The aim of the 2nd consensus meeting was to obtain a North American perspective on the same

four points including the results of the first meeting. Specific questions addressed were:

- Should any items excluded at the first meeting be retained?
- Do all items fit in their domains?
- Should any combined items form their own domain?
- Is the name for each domain appropriate?

MATERIALS AND METHODS

Initial steps

An overview of our COS development methodology highlighting the contribution of the in-person consensus meetings can be found in figure 1. Initiatives including Core Outcome Measures in Effectiveness Trials (COMET),¹⁴ Outcome Measures in Rheumatology (OMERACT)¹⁹ and Harmonizing Outcome Measures for Eczema (HOME)¹⁰ provided methodological guidance that was used and adapted by our HS COS group. Prior to the current study a list of 56 candidate items was identified by combining three data sets: (1) a systematic review of literature, (2) US and Danish qualitative interview studies involving HS patients, and (3) an online HCP item generation survey. More details for these phases can be found in our COS development protocol.²⁰

In brief, the online Delphi exercise involved 94 participants (42 HS patients and 52 HCPs) from 19 countries across four continents. In the first two Delphi rounds, participants voted on an unsorted list of candidate items in terms of their importance in being measured as outcomes in all future HS trials. The results of the first two rounds were then used to inform the structure of two consensus meetings, which are reported here.

Study design

The study was international and multi-professional involving patients, dermatologists, cutaneous surgeons, general surgeons, industry representatives and drug regulatory authorities. The study took place at two face-to-face consensus meetings, in September 2016 in Vienna and in October 2016 at an IDEOM meeting in New York. The locations were planned for both Europe and North America to ensure that European and North American patient and HCP opinions from both

continents were incorporated. The meetings were planned by the HISTORIC steering group, consisting of researchers, HS clinicians and a patient research partner.²⁰

Meeting participants

All Delphi participants from the e-Delphi surveys were invited to attend either the first or the second meeting. If attendance in person was not possible, they were invited to join the Vienna meeting via a Skype® connection. Identification and purposive sampling of the e-Delphi participants is described in the study protocol.²⁰ A few additional individuals who had shown an interest in joining the initiative were invited to take part in the second meeting. Our aim was to maintain a 1:1 ratio of patients: HCPs if possible.

Study procedures

An overview of the study procedures can be found in figure 2. Both consensus meetings had the same overall structure. The structure consisted of initial formal presentations, followed by small group work and subsequent plenary sessions, based on nominal group theory.²¹ The spoken language was English. Introductory presentations included a description of the HISTORIC collaboration, a summary of the need for a COS for HS clinical trials, and results from the first two rounds of the online Delphi survey.²⁰ Background information about how the candidate items were identified was also provided, together with an introduction to the small group work designed to generate consensus using nominal group theory. It was stressed that the views of all participants at the meeting, both patients and HCPs, were of equal importance.

The introductory presentations were followed by a series of small group sessions (6 in the first meeting and 3 in the second meeting). For each task, two small groups worked independently and in parallel, supervised by neutral facilitators. Both facilitators were medical doctors and PhD students studying HS, who were not voting in the E-Delphi surveys. The neutral facilitators encouraged contributions from quieter group members. Group members were switched between each session to ensure that different combinations of patients and HCPs were formed; however, each small group contained at least two patients so that HCPs did not dominate the discussion.

Physical cards, one for each item, were placed on the table for each small group to provide a visual aid for the discussion. On the front of each card was the name and a description of

an item and on the reverse side were summary statistics of the votes cast for the item in the preceding e-Delphi exercise, subdivided by patients and HCPs. Each small group session lasted 20-40 minutes.

Results from each of the two small groups were presented to all participants in subsequent plenary sessions, stimulating discussion if there were differences between the groups. Consensus was sought by discussion, without preceding voting. If consensus was not reached through discussion then no decision was imposed, for example when discussing an item for possible exclusion if no consensus was reached then the item was retained.

The two meetings were similar in structure but differed slightly in the required tasks. Tasks for the first meeting were ranking of the items in order of priority, identifying items that could be excluded, grouping of remaining items into domains and ranking of domains in order of priority. The second meeting was asked to mirror the first by considering if any excluded items should be retained, checking whether participants agreed with the item combinations that were put forward by the first meeting to form domains, and considering whether the domain names were appropriate.

Next steps

Findings from both meetings will be used to form the basis of subsequent online Delphi surveys to obtain consensus from the wider group of stakeholders involved in the process. Based on our protocol, all decisions taken at the meetings need to be confirmed by the larger Delphi group before they are implemented because only a sub-set of the e-Delphi group could contribute to the in-person meetings.

RESULTS

Participants

A list of study participants subdivided by stakeholder group, country and gender can be found in table 1.

The HISTORIC consensus meeting I had 19 participants (5 patients, 14 HCPs) from 11 countries across four continents, the majority being European. The HISTORIC consensus meeting II had 25 participants (6 patients, 19 HCPs), the majority being North American.

The 11 participating HS patients represented six different patient organisations. One additional Canadian patient participated in the first meeting via a Skype ® connection. The participating HCPs were dermatologists (n=14), dermatologic surgeons (n=5), FDA representatives (n=2), pharmaceutical industry representatives (n=2), epidemiologists (n=3), and non-voting (in e-Delphi) steering group members/facilitators (n=4). For comparison, the 52 HCPs included in the E-Delphi round one were dermatologists (n=41), dermatologic surgeons (n=5), medical regulators (n=1), nurses (n=4) and pharmaceutical industry representatives (n=1).

Excluded items

The comprehensive list of unsorted items (n=57) that the participants evaluated is shown in Table 2. Nine items were marked for exclusion the HISTORIC consensus meeting I due to lack of relevance, being unrelated to measurement of disease severity, or not directly linked to the disease. A list of the nine items that the participants agreed to exclude, together with arguments for their exclusion can be found in Table 3. Some participating HCPs spoke in favour of excluding coping, itch and fatigue, but participating patients did not approve and the items were retained.

At the HISTORIC consensus meeting II, there was consensus that all of the items identified at the first meeting were appropriately designated for exclusion. However, it was agreed that the biomarker item should be marked as an area of specific future research interest. It was noted that if, in the future, a biomarker is proven to be strongly related to disease activity or treatment response then the biomarker item/domain should be reconsidered for inclusion in the core domain set.

Grouping of items into domains and naming domains

Creation of potential domains was achieved by three small group and plenary sessions at the HISTORIC consensus meeting I, producing consensus to group the items into nine domains (Table 4). These domains and their contributing items were reviewed during two sessions at the HISTORIC consensus meeting II. HISTORIC consensus meeting II participants recommended switching, the 'number of chronic areas' item from the 'physical signs' domain to the 'disease course' domain, as the item would be reported by the patient rather than being measured by the physician. It was highlighted that the term 'chronic' in this context needs to be defined further and this issue was marked as a future task for the HISTORIC project. The group provisionally

agreed that 'chronic' relates to a duration of at least 6 weeks.

Both working groups at consensus meeting II independently agreed to rename the 'decreased mobility' item as 'physical functioning' and to combine this domain with the 'psychological-social' domain to form a 'HS-specific quality of life' domain. Participants emphasized that it is crucial that this domain should capture the specific aspects of the patient's quality of life that are affected by HS, so a generic health related quality of life domain would not be sufficient.

Another recommendation from meeting II was to group together the 'patient global assessment' and 'physician global assessment' domains to produce a single 'global assessment' domain encompassing both the patient and HCP perspective. This fusion and the global assessment items/domains themselves were heavily debated. Some participants felt that the global assessments should be excluded altogether, because, by definition, global assessment provides a relatively non-specific overview of disease severity. Others spoke in favour of global assessments because they considered a global anchor to be very useful. Another argument in favour of retaining global assessments is that these domains are considered important by the FDA. Creation of a single 'global assessment' domain was suggested by a group member and supported by the rest of the group based on the concept that both the patient and HCP global perspectives are important and should be assessed in a similar manner.

After HISTORIC consensus meeting II, there was consensus to suggest seven core domains: disease course, physical signs, HS-specific quality of life, satisfaction, symptoms, pain, and global assessments (Table 5).

DISCUSSION

In total, 41 stakeholders including patients, dermatologists, (dermatologic) surgeons, epidemiologists, statisticians, pharmaceutical industry representatives and drug regulatory representatives participated in the HISTORIC consensus meetings I and II. Important progress was made towards reaching global consensus on core outcomes for HS clinical trials. Seven potential core domains were put forward for consideration by the larger e-Delphi consensus group in subsequent E-Delphi surveys.

Our study differs from other COS processes in that our domains were developed through in-person discussion, combining items from a comprehensive list of candidate items. This

discussion was guided by votes cast in preceding e-Delphi surveys. In most previous studies, domains are created by the steering committee alone without broader dialogue with Delphi participants before the first round of the Delphi survey is launched. The concept of involving more patients and other Delphi participants in the creation of the domains is based on the principle of inclusivity, in keeping with the philosophy of our HISTORIC initiative. Feedback from stakeholders was very positive and the general view was that an inclusive approach is important to ensure relevance to patients and subsequent global acceptance and use of the HS COS by clinical trial designers.

One methodological limitation is that it was not possible to have all e-Delphi participants present at the meetings, and therefore it was not possible to incorporate everyone's opinion in the formation of domains. To mitigate for this, the next step will be to ask the larger e-Delphi group if they agree with the decisions made at the meetings in an evaluation and confirmation survey. After this, the next planned steps are to perform two additional E-Delphi rounds. The results from these rounds will finalise the core domain set, having built on the work from our in-person consensus meetings.

Another limitation to the study is that we did not reach our aim of a 1:1 ratio of participating patients:HCPs. Most of the participating patients were however representatives from HS patient associations and were able to represent a full cross-section of HS patients in terms of demographics and disease severity. Meeting facilitators ensured that patients provided equal input compared to HCPs, even though they were outnumbered by the HCPs, by encouraging patient involvement in every aspect of the discussion.

With the present study, we have come a lot closer to global consensus on a COS for HS research. The number of randomised controlled trials of HS therapy is still limited. However, interest in the disease is growing and the number of trials planned is considerable. The development of a COS is thus particularly timely for HS, and a HS COS should substantially improve future HS trial design.

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FIGURE LEGENDS

Fig 1. Summary of the HS Core domain development process, with a highlight of the part described in this study

Fig 2. Summary of study procedures. See text for details.

| Participants | HISTORIC Consensus meeting I Vienna | HISTORIC Consensus meeting II New York |
|--|---|--|
| Subdivided by stakeholder group (n) | | |
| Patients | 5 | 6 |
| Health care professionals: | | |
| Dermatologist HS experts | 8 | 8 |
| Cutaneous surgeons | 3 | 2 |
| Statisticians | 0 | 1 |
| Epidemiologists | 0 | 2 |
| FDA representatives | 0 | 2 |
| Pharmaceutical industry | 0 | 2 |
| Steering group/facilitators not included above | 3 | 2 |
| | | |
| Patients subdivided by country (n) | | |
| Belgium | 1 | 0 |
| Canada* | 0 | 3 |
| Denmark | 1 | 0 |
| United Kingdom | 3 | 3 |
| USA | 0 | 0 |
| | | |
| HCPs subdivided by country (n) | | |
| Australia | 1 | 0 |
| Canada | 0 | 4 |
| Denmark | 3 | 2 |
| Germany | 1 | 0 |
| Israel | 0 | 1 |
| Malaysia | 2 | 0 |
| Poland | 1 | 0 |
| Sweden | 1 | 0 |
| the Netherlands | 3 | 0 |
| United Kingdom | 1 | 1 |
| USA | 1 | 11 |
| | | |
| Subdivided by gender | | |
| Male n (%) | 11(58%) | 9(36%) |
| | | |
| Total number | 19 | 25 |

*One patient from Canada participated in the first meeting via a Skype connection

Table 1 Study participants subdivided by stakeholder group, country and gender. Three members from the HISTORIC steering group (From UK, USA and Denmark) participated in both meetings and are thus represented twice in the table.

| Item | | Help text | Item | | Help text |
|------|--|--|------|--------------------------------|--|
| 1 | Biomarkers | Measures of disease presence or activity in blood samples | 30 | Dyspigmentation | Changes (lighter or darker) to the normal colour of your skin |
| 2 | Drainage | Secretion, blood, stains, suppuration | 31 | Anatomic location | Body areas and number of body areas involved |
| 3 | Edema | Swelling of the skin | 32 | Number of inflamed nodules | Number of red, painful or tender nodules |
| 4 | Economic burden | Economic burden to the patient related to the disease (e.g., doctor appointments, surgery, medication), management (e.g., bandages, pads, or diet), time lost | 33 | Psychological functioning | Feelings of depression, apathy, loneliness, suicidal thoughts. Feelings of irritation, anxiety, stress |
| 5 | Coping | Being able to handle (cope with) having the disease | 34 | Health related Quality of life | Perceived physical, mental and social health over time |
| 6 | Odour | Unpleasant odour | 35 | Number of fistulae | Number of connections to skin surface |
| 7 | Satisfaction with treatment | Satisfaction with effectiveness; time spent on treatment | 36 | Pain | Pain |
| 8 | Adverse effects of surgical treatments | All types of side effects from surgical treatments (e.g. bleeding, infection, contractures) | 37 | Cognition | Impact on concentration (e.g. at work or at school, or in leisure activities) |
| 9 | Number of cysts | Number of sac-like pockets under the skin which contain fluid or debris from the skin | 38 | Fatigue | Physical weariness sometimes combined with mental weariness |
| 10 | Comorbidities | Associated diseases e.g. metabolic syndrome, PCOS or other inflammatory diseases | 39 | Cosmesis | Visual appearance of a person's skin from his/her own perspective related to the disease and surgery for the disease |
| 11 | Intimacy | Impact on sexual having desire or feeling desired, pain during sexual activity, abstaining from sex, fear of being rejected | 40 | Patient global evaluation | Overall assessment of the disease from the perspective of the patient himself or herself, alone and without the influence of anyone else |
| 12 | Ability to work or study | Ability to work or study, ability to gain or keep employment, influence on type of job or study, time off from work or study, impact on career | 41 | Washing or Bathing | Ability to wash or bathe oneself; having to frequently wash or bathe oneself |
| 13 | Adverse effects of medical treatments | All types of side effects from medical treatments | 42 | Ulceration | Absence of upper layers of the skin forming an ulcer |
| 14 | Number of non-inflamed nodules | Number of skin coloured nodules which may not be painful or tender | 43 | Physician global evaluation | Overall assessment of the disease from the perspective of the physician alone |
| 15 | Itch | Itch | 44 | Number of sinus tracts | Number of tunnel-like connections between lesions |
| 16 | Self-treatment, not prescribed | Self-treatment which is not prescribed (e.g. self-incision to obtain pain relief, placing ice cubes or warm compresses on boils) | 45 | Scarring from surgery | Scars resulting from surgery |
| 17 | Number of abscesses | Number of collections of pus (sterile or infected) | 46 | Compliance | A patient's adherence to a recommended course of treatment |
| 18 | Total lesion count | Total number of all types of lesions | 47 | Satisfaction with care | Access to care, satisfaction with the doctor's knowledge of disease, quality of care, feeling supported by medical personnel |
| 19 | Psychosocial functioning | Feelings of being accepted by others, nervous to be in public, withdrawn from relationships | 48 | Independence | Need to be independent, not to dependent on others |
| 20 | Scarring from HS | Scar formation in involved areas | 49 | Time to post-op recovery | Time to healing after surgery |
| 21 | Need for treatment and bandages | Requirements for prescribed treatment, e.g. acute treatment, pain killers, topical treatment, in-hospital treatment and bandages | 50 | Clothing restrictions | Impact on choice of clothing (e.g. choosing clothes that do not irritate lesions, that cover lesions, that cover stains) |
| 22 | Surface area | Area of the skin surface involved | 51 | Flare frequency | Frequency of flares |
| 23 | Impact on close relationships | Impact on relationship to partner or family member, neglect of family, poor understanding of disease by family | 52 | Inflammatory lesion count | Total number of all red, painful or tender lesions (abscesses or inflamed nodules) |
| 24 | Time to recurrence | Time to reappearance of activity, such as after surgery or after ending medical therapy | 53 | Comedones | Appearance of small "blackheads" on the surface of the skin formed by the blockage of pores |
| 25 | Emotional well-being | Feelings of powerlessness, embarrassment, low self-esteem | 54 | Constitutional symptoms | The experience of one or more symptom(s) associated with the development of new lesions (e.g. fatigue, fever-like sensation, headache) |
| 26 | Decreased mobility | Decreased mobility, skin tightness, may be associated with restrictions in exercising, walking, reaching out, standing, sitting, activities of daily living (e.g. housework) | 55 | Erythema | Redness of the skin |
| 27 | Satisfaction with social roles | Satisfaction with oneself as a partner, parent, family member, friend, or colleague | 56 | Sleep-disturbance | Difficulty sleeping, inability to sleep, poor quality of sleep |
| 28 | Progression of course | Worsening of disease, prevention of worsening | 57 | Number of chronic areas | Number of chronic areas open for more than 6 weeks |
| 29 | Recreation and leisure activity | Interference with leisure/recreational activities (e.g., sports, do-it-yourself, playing instruments, scouting, hiking or outdoor life). Interference with planning of such activities | | | |

Table 2 List of all items included in the Delphi exercise (item 57 included after the first round). The Help text was shown with each item in the e-Delphi as well as on the cards that were used for the small group work at the meetings. The items numbers generated at random before round one of the e-Delphi.

| Item (help text) | Reasoning for exclusion (agreed by patients and HCPs) |
|---|---|
| Self-treatment – not prescribed (Self-treatment which is not prescribed (e.g. self-incision to obtain pain relief, placing ice cubes or warm compresses on boils) | Too non-specific, difficult to measure |
| Biomarkers (Measures of disease presence or activity in blood samples) | For HS, there is no biomarker proven to be strongly related to disease activity and treatment response |
| Cosmesis (Visual appearance of a person's skin from his/her own perspective related to the disease and surgery for the disease) | Participating patients felt that this item was not as important as other items, and felt that cosmesis was covered by other items such as scarring and number of sinus tracts |
| Washing or bathing (Ability to wash or bathe oneself; having to frequently wash or bathe oneself) | Very individual. Could be an instrument to measure drainage, but would then be covered by the drainage item |
| Comedones (Appearance of small "blackheads" on the surface of the skin formed by the blockage of pores) | Participants, especially patients, felt that this item was not important enough to be a core outcome for trials |
| Dyspigmentation (Changes (lighter or darker) to the normal colour of your skin) | Participants, especially patients, felt that this item was not important enough to be a core outcome for trials |
| Satisfaction with care (Satisfaction with oneself as a partner, parent, family member, friend, or colleague) | Not likely to be directly affected as an outcome by any intervention. Often depends on individual doctor-patient relationships |
| Economic burden (Economic burden to the patient related to the disease (e.g., doctor appointments, surgery, medication), management (e.g., bandages, pads, or diet), time lost) | Difficult to measure, varies a lot from country to country, in trials treatment expenses are covered |
| Comorbidities (Associated diseases e.g. metabolic syndrome, PCOS or other inflammatory diseases) | Not fair to include comorbidities as core outcomes as some treatments might improve HS but not the comorbidities. Comorbidities that might result from treatment should be captured as adverse events |

Table 3 Items marked for exclusion at HISTORIC consensus meeting I and II with the arguments for their exclusion

| Domain | Included items (help text) |
|--------------------------------|--|
| 1. Disease course | <p>Progression of course (Worsening of disease, prevention of worsening)</p> <p>Time to recurrence (Time to reappearance of activity, such as after surgery or after ending medical therapy)</p> <p>Flare frequency and duration (Frequency and duration of flares)</p> |
| 2. Physical signs | <p>Total lesion count (Total number of all types of lesions)</p> <p>Inflammatory lesion count (Total number of all red, painful or tender lesions (abscesses or inflamed nodules))</p> <p>Number of inflamed nodules (Number of skin coloured nodules which may not be painful or tender)</p> <p>Number of non-inflamed nodules (Number of skin coloured nodules which may not be painful or tender)</p> <p>Number of abscesses (Number of collections of pus (sterile or infected))</p> <p>Number of fistulae (Number of connections to skin surface)</p> <p>Number of sinus tracts (Number of tunnel-like connections between lesions)</p> <p>Ulceration (Absence of upper layers of the skin forming an ulcer)</p> <p>Edema (Swelling of the skin)</p> <p>Number of cyst (Number of sac-like pockets under the skin which contain fluid or debris from the skin)</p> <p>Erythema (Redness of the skin)</p> <p>Anatomic location (Body areas and number of body areas involved)</p> <p>Surface area (Area of the skin surface involved)</p> <p>Scarring from HS (Scar formation in involved areas)</p> <p>Number of chronic areas (Number of chronic areas open for more than 6 weeks)</p> |
| 3. Psychological-social | <p>Coping (Being able to handle (cope with) having the disease)</p> <p>Emotional well-being (Feelings of powerlessness, embarrassment, low self-esteem)</p> <p>Sleep-disturbance (Difficulty sleeping, inability to sleep, poor quality of sleep)</p> <p>Ability to work or study (Ability to work or study, ability to gain or keep employment, influence on type of job or study, time off from work or study, impact on career)</p> <p>Independence (Need to be independent, not to dependent on others)</p> <p>Satisfaction with social roles (Satisfaction with oneself as a partner, parent, family member, friend, or colleague)</p> <p>Psychosocial functioning (Feelings of being accepted by others, nervous to be in public, withdrawn from relationships)</p> <p>Psychological functioning (Feelings of depression, apathy, loneliness, suicidal thoughts. Feelings of irritation, anxiety, stress)</p> <p>Intimacy (Impact on sexual having desire or feeling desired, pain during sexual activity, abstaining from sex, fear of being rejected)</p> <p>Recreation (Interference with leisure/recreational activities (e.g., sports, do-it-yourself, playing instruments, scouting, hiking or outdoor life). Interference with planning of such activities)</p> <p>Impact on close relationships (Impact on relationship to partner or family member, neglect of family, poor understanding of disease by family)</p> <p>Cognition (Impact on concentration (e.g. at work or at school, or in leisure activities))</p> <p>Clothing restrictions (Impact on choice of clothing (e.g. choosing clothes that do not irritate lesions, that cover lesions, that cover stains))</p> |
| 4. Satisfaction | <p>Satisfaction with treatment (Satisfaction with effectiveness; time spent on treatment)</p> <p>Compliance (A patient's adherence to a recommended course of treatment)</p> <p>Adverse effects of medical treatments (All types of side effects from medical treatments)</p> <p>Adverse effects of surgical treatments (All types of side effects from surgical treatments (e.g. bleeding, infection, contractures))</p> <p>Scarring from surgery (Scars resulting from surgery)</p> <p>Time to post-op recovery (Time to healing after surgery)</p> <p>Need for treatment and bandages (Requirements for prescribed treatment, e.g. acute treatment, pain killers, topic treatment, in-hospital treatment and bandages)</p> |
| 5. Symptoms | <p>Constitutional/prodromal (The experience of one or more symptom(s) associated with the development of new lesions (e.g. fatigue, fever-like sensation, headache)</p> <p>Fatigue (Physical weariness sometimes combined with mental weariness)</p> <p>Itch (Itch)</p> <p>Odour (Unpleasant odour)</p> <p>Drainage (Secretion, blood, stains, suppuration)</p> |
| 6. Decreased mobility | <p>Decreased mobility (decreased mobility, skin tightness may be associated with restrictions in exercising, walking, reaching out, standing, sitting, activities of daily living (e.g. housework))</p> |
| 7. Pain | <p>Pain</p> |
| 8. Patient global assessment | <p>Patient global assessment (Overall assessment of the disease from the perspective of the patient himself or herself, alone and without the influence of anyone else)</p> |
| 9. Physician global assessment | <p>Physician global assessment (Overall assessment of the disease from the perspective of the physician alone)</p> |

Table 4 Results of HISTORIC consensus meeting I in Vienna: list of created domains and their included items

| Domain | Included items (help text) |
|--|--|
| 1. Disease course | <p>Progression of course (Worsening of disease, prevention of worsening)</p> <p>Time to recurrence (Time to reappearance of activity, such as after surgery or after ending medical therapy)</p> <p>Flare frequency and duration (Frequency and duration of flares)</p> <p>Number of chronic areas* (Number of chronic areas open for more than 6 weeks)</p> |
| 2. Physical signs | <p>Total lesion count (Total number of all types of lesions)</p> <p>Inflammatory lesion count (Total number of all red, painful or tender lesions (abscesses or inflamed nodules))</p> <p>Number of inflamed nodules (Number of skin coloured nodules which may not be painful or tender)</p> <p>Number of non-inflamed nodules (Number of skin coloured nodules which may not be painful or tender)</p> <p>Number of abscesses (Number of collections of pus (sterile or infected))</p> <p>Number of fistulae (Number of connections to skin surface)</p> <p>Number of sinus tracts (Number of tunnel-like connections between lesions)</p> <p>Ulceration (Absence of upper layers of the skin forming an ulcer)</p> <p>Edema (Swelling of the skin)</p> <p>Number of cyst (Number of sac-like pockets under the skin which contain fluid or debris from the skin)</p> <p>Erythema (Redness of the skin)</p> <p>Anatomic location (Body areas and number of body areas involved)</p> <p>Surface area (Area of the skin surface involved)</p> <p>Scarring from HS (Scar formation in involved areas)</p> |
| 3. HS specific quality of life* | <p>Coping (Being able to handle (cope with) having the disease)</p> <p>Emotional well-being (Feelings of powerlessness, embarrassment, low self-esteem)</p> <p>Sleep-disturbance (Difficulty sleeping, inability to sleep, poor quality of sleep)</p> <p>Ability to work or study (Ability to work or study, ability to gain or keep employment, influence on type of job or study, time off from work or study, impact on career)</p> <p>Independence (Need to be independent, not to dependent on others)</p> <p>Satisfaction with social roles (Satisfaction with oneself as a partner, parent, family member, friend, or colleague)</p> <p>Psychosocial functioning (Feelings of being accepted by others, nervous to be in public, withdrawn from relationships)</p> <p>Psychological functioning (Feelings of depression, apathy, loneliness, suicidal thoughts. Feelings of irritation, anxiety, stress)</p> <p>Intimacy (Impact on sexual having desire or feeling desired, pain during sexual activity, abstaining from sex, fear of being rejected)</p> <p>Recreation (Interference with leisure/recreational activities (e.g., sports, do-it-yourself, playing instruments, scouting, hiking or outdoor life). Interference with planning of such activities)</p> <p>Impact on close relationships (Impact on relationship to partner or family member, neglect of family, poor understanding of disease by family)</p> <p>Cognition (Impact on concentration (e.g. at work or at school, or in leisure activities))</p> <p>Clothing restrictions (Impact on choice of clothing (e.g. choosing clothes that do not irritate lesions, that cover lesions, that cover stains)</p> <p>Physical functioning* (decreased mobility, skin tightness may be associated with restrictions in exercising, walking, reaching out, standing, sitting, activities of daily living (e.g. housework)</p> |
| 4. Satisfaction | <p>Satisfaction with treatment (Satisfaction with effectiveness; time spent on treatment)</p> <p>Compliance (A patient's adherence to a recommended course of treatment)</p> <p>Adverse effects of medical treatments (All types of side effects from medical treatments)</p> <p>Adverse effects of surgical treatments (All types of side effects from surgical treatments (e.g. bleeding, infection, contractures)</p> <p>Scarring from surgery (Scars resulting from surgery)</p> <p>Time to post-op recovery (Time to healing after surgery)</p> <p>Need for treatment and bandages (Requirements for prescribed treatment, e.g. acute treatment, pain killers, topic treatment, in-hospital treatment and bandages)</p> |
| 5. Symptoms | <p>Constitutional/prodromal (The experience of one or more symptom(s) associated with the development of new lesions (e.g. fatigue, fever-like sensation, headache)</p> <p>Fatigue (Physical weariness sometimes combined with mental weariness)</p> <p>Itch (Itch)</p> <p>Odour (Unpleasant odour)</p> <p>Drainage (Secretion, blood, stains, suppuration)</p> |
| 6. Pain | Pain |
| 7. Global assessments* | <p>Patient global assessment (Overall assessment of the disease from the perspective of the patient himself or herself, alone and without the influence of anyone else)</p> <p>Physician global assessment (Overall assessment of the disease from the perspective of the physician alone)</p> |

*Domains/items that were changed or moved at HISTORIC consensus meeting II compared with consensus meeting I

Table 5 Results of HISTORIC consensus meeting II: list of created domains and their included items